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(54) DIALYSIS APPARATUS WITH SELECTIVE CHEMICAL ACTIVITY

(71) I. VIKTOR HOLGER HYDÉN, a Swedish subject, of Geijersgatan 6, 411 34 Göteborg, Sweden, hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to dialysis apparatus, such as apparatus for haemodialysis, but can also be used for purification of liquids other than blood.

In this specification, various dialysis devices are described, including those that are previously known and the apparatus according to the invention, emphasis being laid on so-called artificial kidneys. It should, however, be noted that the apparatus according to the invention, like other known dialysis apparatus, also can be used for purification of liquids other than blood.

It has been known for a relatively long time that patients suffering from an acutely or chronically failing kidney function can be treated with an artificial kidney which, during the healing period or while waiting for a suitable kidney transplant, performs the function of the natural kidney to eliminate urea and other undesirable constituents in the blood. The patient's blood flows from an artery through the artificial kidney and returns to a vein by means of an extracorporeal shunt. The original design of artificial kidney, of which a plurality of improved variants are still predominantly in use for haemodialysis, is a dialysis apparatus having a semipermeable membrane which separates a blood stream from a dialysate stream in such a manner that undesirable substances, as well as some desirable substances, in the blood pass through the pores of the dialysis membrane to the dialysate. This is a purely physical process without any kind of chemical activity. These original devices

were very large and heavy units, which contained up to 1,000 litres of dialysate and were both expensive and labour-demanding. Consequently, only a limited number of dialysis centres could be established in special clinics. Due to successive improvements of the original designs, including the provision of an improved dialysis membrane, pre-fabricated sterile disposable membrane packs, improved instrumentation etc., improved dialysis apparatus has been developed which today is more compact and shows better dialysis results whilst incurring lower initial and operational costs. Notwithstanding these improvements, a dialysis apparatus is still relatively large and expensive, and requires specially trained personnel for its operation in hospitals provided with specially equipped rooms.

As further development of a purely physical dialysis apparatus can probably result only in marginal improvements, development has recently turned in new directions. By combining dialysis with various kinds of chemical activity, it has been possible to improve the dialysis result and at the same time diminish the dimensions of the dialysis apparatus. Moreover, the range of medical application for dialysis apparatus has been widened beyond dialysis at kidney failure. Among known devices, chemical activity is assigned mainly to the dialysate part or, in some cases, to an ultrafiltrate, which subsequent to chemical treatment is returned to the patient's blood stream.

Continuous chemical purification of the dialysate enables the amount of dialysate to be reduced to a few litres and thereby renders it possible to design dialysis devices with considerably smaller dimensions than previously. The purification of the dialysate takes place in principle, as follows. Urea transferred from the blood to

the dialysate is degraded selectively by the enzyme urease to ammonium carbonate whereafter ammonium ions and other undesirable constituents separated from the blood are removed by adsorbents. The adsorbents, usually are specific ones and have been pre-conditioned by known methods so as to remove the undesirable constituents, while the constituents desirable for the dialysate, e.g. chloride ions, remain in the dialysate. Known adsorbents are anionic and cationic exchange resins, zirconium phosphate, zirconium oxide and activated carbon.

The widened medical application range is related to such a form of enzyme therapy, the object of which is selectively to remove undesirable proteins from the blood for therapeutical purposes, for example to degrade asparagine by means of L-asparaginase, as this was found to have a therapeutical effect on certain forms of cancer. Thereby, not only kidney failure is made accessible to treatment by a dialysis apparatus, but also, in principle, all pathological conditions, in which a therapeutical effect can be achieved by separating from the blood at least one undesirable constituent by means of a dialysis membrane, whereafter this constituent is selectively degraded on the dialysate side by an enzyme. Certain enzymes have a toxic effect and this is the reason why enzymes are not used in contact with the blood in such apparatus.

The following U.S. Patent Specifications provide examples of known dialysis devices combined with chemical activity. U.S. Patent Specification No. 3,608,729 shows that it is known to purify a non-circulating dialysate by means of adsorbents which are packed into pockets formed by a profiled dialysis membrane. An ion exchange resin is used as adsorbent, optionally in combination with activated carbon and an enzyme, for example urease, to degrade urea. A vibrator is proposed to facilitate the transport of the constituents to be separated from the dialysate to the adsorbent. U.S. Patent Specification No. 3,617,545 shows an electro-dialyzer for the purification of dialysate and, alternatively, an ultrafiltrate (blood plasma) which contains constituents having molecular weights up to 70,000, in several steps, comprising demineralization, degradation of urea by means of urease, cation exchanger for adsorption of ammonium ions, remineralization, adsorption of uric acid and creatinine with activated carbon and adsorption of sulphate and phosphate ions by means of an anion exchanger.

U.S. Patent Specification No. 3,619,423 shows a cascade dialysis apparatus for purification of blood, in which apparatus a

dialysis section and an ultrafilter utilize one and the same recirculating dialysate, and each contains a dialysis membrane of which the pores permit substances with molecular weights up to 10,000 to pass. An undesirable constituent in the blood, which can pass through the membrane of the dialysis section into the dialysate and is to be selectively separated for a therapeutical purpose, is degraded with the corresponding enzyme which is dissolved in the dialysate. The constituents desirable for the blood are returned to the blood through the membrane of the ultrafilter which does not permit the passage of enzymes since these have molecular weights of about 100,000. The circulating dialysate is purified continuously by specific or non-specific adsorbents of a kind not stated in detail. The reduction of the asparagine content of the blood by means of L-asparaginase is mentioned as an example of chemotherapy for cancer. U.S. Patent Specification No. 3,669,878 finally, shows a dialysate purification device for a conventional dialysis apparatus. The purification device, designed as a column through which the dialysate flows, is connected in series to the circuit of the dialysate. The column is filled with an inorganic adsorbent, zirconium phosphate, on which urease is adsorbed. The urease enzymatically degrades urea to ammonium carbonate. The zirconium phosphate acts as an ion exchanger and adsorbs the ammonium ions, whereby sodium ions, which were adsorbed on the zirconium phosphate, are released according to a reaction formula shown. The sodium ions are not harmful since they normally exist in great amounts in the dialysate.

In spite of the additional improvements obtained by the introduction of chemical activity in combination with dialysis, a dialysis apparatus for haemodialysis is still relatively large, expensive and technically complicated, and is neither suitable nor possible to use for home dialysis. A further disadvantage of known apparatus is that the pore size of the dialysis membranes must be limited to the passage of substances having molecular weights of up to 2,500-3,000 in order to prevent the loss in the dialysate of excessive amounts of constituents which have a low molecular weight and are desirable in the blood. When, however, the afore-described method with an ultrafilter is used, the pore size can be increased to exemplified molecular weights of between 10,000-70,000. Alternatively, in a conventional dialysis apparatus with filters having larger pores, it is possible to balance the increased loss of desirable constituents in the blood by adding an excess

of these constituents to the dialysate. Both said alternatives result primarily in higher dialysis costs. When an ultrafilter is introduced, the apparatus increases in size and becomes more expensive and more complicated. It is uneconomic to add the desirable constituents, of which for example water soluble proteins are expensive, to a relatively great amount of dialysate. There is evidence that impurities are found in the blood which have an incompletely known composition and molecular weights of between 10,000-15,000. According to an ever widely spread opinion in the large kidney clinics, a better dialysis result would probably be achieved if these impurities could also be removed. An increase in pore size would also facilitate passage through the dialysis membrane and would consequently shorten the time necessary for dialysis. A further disadvantage of known devices for haemodialysis is that the utilization of enzymes for the selective separation of undesirable constituents from the blood for therapeutical purposes is restricted to the dialysate side. This restriction is due to several enzymes having an antigenic or other toxic effect on the blood, for which reason a direct contact between blood and enzyme has to be avoided because no safe method is known in the prior art for insolubilizing the enzymes having maintained chemical activity. Several of the constituents to be selectively separated have relatively high molecular weights and consequently pass slowly through the pores of the dialysis membrane, so that the separation on the dialysate side takes more time than it would require with direct contact between blood and enzyme. It is, therefore, desirable during haemodialysis only to use in contact with the blood those enzymes which have no toxic properties.

45 All this remarkable development work has resulted in better, simpler and cheaper haemodialysis, but the known dialysis apparatus with associated peripheral equipment still requires much space and is still both expensive and complicated. At the same time there is a demand partly to improve the dialysis result and partly to widen the application range in chemotherapy. It is a matter of great interest, particularly with respect to dialysis for kidney failure, to develop a simple, cheap, easy-to-service dialysis apparatus with good dialysis properties, which apparatus would render it possible to increase the number of dialysis treatments in hospitals at maintained costs and also in suitable cases to perform the dialysis at home.

It is an object of the present invention to mitigate the aforescribed and other

disadvantages involved with known dialysis apparatus and, in particular, with an artificial kidney.

According to the invention a dialysis apparatus with selective chemical activity, such as an artificial kidney, includes a semipermeable dialysis membrane forming a partition between the liquid to be dialyzed and a dialysate, the dialysis membrane being selected to permit the passage of substances with molecular weights of at least 2,500, a first surface of the dialysis membrane facing the dialyzed liquid, a second surface of the dialysis membrane facing the dialysate, at least one of said surfaces being coated with at least one selectively chemically active substance insolubilized on the surface, and at least one selectively acting adsorbent being provided in the circuit of the dialysate. The dialysis membrane is preferably selected to permit the passage of substances with a molecular weight of up to 10,000 or up to 15,000. The chemically active substance is preferably an enzyme or other protein, or an anti-biotic.

The dialysis membrane is preferably in the form of a flattened tube, a spacing member having an open structure carrying an adsorbent or a mixture of adsorbents, and the dialysis membrane and the spacing member being wound helically together. Alternatively, the dialysis membrane may be of a flat shape and be placed adjacent a distance member of similar shape.

The dialysis membrane preferably consists of a material of which the surface is so prepared by hydrolysis or another known method that it shows an increased number of hydroxyl groups or other groups for rendering possible the insolubilization of enzymes and antibiotics and other proteins in a great amount.

The spacing member preferably consists of a base provided with fine perforations, and an open support and spacing structure secured to the base which defines ridges extending at an oblique angle to the longitudinal direction of the spacing member. Alternatively, the spacing member may be formed as a plastics-bonded, thin, flexible beam with a generally I-shaped cross-section moulded from a fibrous material.

The adsorbent may consist of pre-conditioned zirconium phosphate and/or zirconium oxide or of pre-conditioned zirconium phosphate and/or zirconium oxide in combination with activated carbon. A purifying cartridge containing the adsorbent is preferably provided in a return flowpath of the dialysate.

A preferred embodiment of the invention is now described, by way of example only, with reference to the accompanying drawings, in which:—

Figure 1 is a diagrammatic side elevation showing the basic layout of a dialysis apparatus;

Figure 2 is a perspective elevation of a dialysis apparatus;

Figure 3 is a perspective view of a dialysis cylinder shown partially cut away;

Figure 4 is a perspective view of the dialysis cylinder illustrated in Figure 3 but showing connections for blood supply, one connection being shown disconnected;

Figure 5 is an exploded perspective view of a section of a dialysis hose with associated spacing members;

Figure 6 is a perspective view of a portion of the spacing member shown in Figure 5, with its adsorbent carrying part being partially exposed;

Figure 7 is a perspective view of a section of an alternative embodiment of a spacing member;

Figure 8 is a horizontal cross-section through mounted spacing members according to Figure 7;

Figures 9 and 10 are respectively, perspective and sectional views of a spectrometer;

Figure 11 is a perspective view of a purifying cartridge with adsorbents, and

Figure 12 is a longitudinal section through a drop dosimeter.

In all Figures the same reference character has been used to identify similar details.

The basic layout of the apparatus is apparent from Figure 1. A dialysis membrane 1 in the form of a flattened tube is helically wound with an intermediate spacing member 2, and is disposed in a cylindrical dialysis container 7 shown in Figure 2. The interior of the hose-shaped dialysis membrane 1 forms an active part of an inner circuit for the liquid to be dialysed. The space formed by the spacing member 2 between the turns of the membrane 1 constitutes an active part of an outer circuit for the dialysate 8. The two circuits are connected in counter-flow relationship. The inner circuit is provided with a supply hose 3 and an outlet hose 4 which, for the dialysis of blood, would be connected respectively to an artery and to a vein. A dialysate container 9 is positioned in the outer circuit for the dialysate 8 and is provided with a pump 10 for circulating the dialysate 8 through a supply hose 5 to the dialysis part of the outer circuit, from which the dialysate is returned through a return hose 6 connected to a purification cartridge 11 immersed in the dialysate container 9. The return hose 6 extends through a hole provided in the beam path of a spectrometer 12 which is arranged in a known electronic circuit including an optical and/or acoustic alarm

device for providing alarm if blood or haemoglobin appears in the dialysate 8. A thermostatically controlled heating device 14 is provided in the dialysate container 9 to maintain the dialysate at body temperature. An exchangeable drop dosimeter 13 of known kind is mounted on the dialysate container 9 and enables a continuous supply of additives to be made to the dialysate. As designated by E in Figure 1, an active substance such as enzyme or antibiotic, depending on the chemical activity desired in the individual case, is insolubilized on the surface included in the inner circuit of the dialysis membrane 1.

These substances can alternatively, in suitable cases, be insolubilized on the dialysis membrane surface facing toward the dialysate 8. Details of the material and pore size of the dialysis membrane are described later. The spacing member 2 has an open structure, into which the adsorbent designated by A is impressed. The purification cartridge 11 also contains adsorbent of the aforesaid kind.

A small electric vibrator 48 is mounted on the outside of the dialysis container in order to accelerate the liquid flow about the dialysis membrane 1 and the adsorbent A, thereby to accelerate the dialysis as well as to prevent the blood from coagulating where the flow velocity is low.

Figure 2 illustrates the arrangement of the components shown in Figure 1 as a compact transportable unit. The lowermost component is the dialysate container 9 which has a cover 15 on which the dialysis container 7 is mounted by supports 16. The pump 10 is mounted directly on the cover 15 together with an instrument box 17 which includes the spectrometer 12 with associated alarm device, for example a buzzer 18 and necessary control means. The drop dosimeter 13 is screwed into one of the pipe sockets 19 provided for this purpose at the upper portion of the dialysate container 9.

In view of the difficulty of providing a flat dialysis hose of sufficient width, the dialysis container 7, as shown in Figures 2-4, contains two helical units which are connected in parallel and each consists of the dialysis membrane 1 and the spacing member 2 of the kind described above with reference to Figure 1. For the inner circuit, i.e. the ends of the hose-shaped dialysis membranes 1, separate connections are provided for the supply and outlet hoses 3 and 4. The supply takes place through a central distribution means, substantially concealed in Figure 2, the outer part of which consists of a supply socket 20 provided on the upper surface of the dialysis container 7 and having two distribution hoses 21 and one branch pipe 50,

to which the supply hose 3 is connected. The concealed part of the distribution means is in principle identical with a corresponding collecting means provided on the surface of the dialysis container 7. The collecting means consists of two connections 22, best seen from Figures 2 and 4, fastened on the shell surface of the dialysis container 7 and connected by means of hoses 23 and 24 to a branch pipe 25, which in its turn is connected to the outlet hose 4. As illustrated in Figure 4, each connection comprises a base 26, a gasket 27, a washer 28, and a hose base 29 which is clamped in the washer 28 for the hose-shaped dialysis membrane 1 and the return hoses 23 and 24 respectively.

Figure 3 shows in the sectional portion how the two helical units formed from the dialysis membrane 1 and spacing member 2 are disposed one upon the other. As shown in Figure 6, the spacing member 2 consists of a base portion 30 which is provided with fine through holes and serves as a carrier for an open structure in the form of ridges 31 fastened thereon and forming an oblique angle (about 45°) with the longitudinal direction of the spacing member 2. As shown in Figure 5, when the dialysis membrane 1 is helically wound between two spacing members, their oblique-angled ridges 31 form in adjacent turns angles with each other. The points of intersection between the ridges 31 located against each other thereby form a chequered pattern of supporting points for the dialysis membrane 1. This arrangement provides in a simple manner both the desired distance between contiguous turns of the dialysis membrane 1, and uniformly distributed supporting points over the entire surface of the dialysis membrane 1. As mentioned before, the open structure in the ridges 31 is filled with the adsorbent or adsorbents used as designated by A in Figure 1.

The spacing member can, alternatively, be designed as a plastics-bonded, thin, flexible I-shaped beam 32 moulded from a fibrous material as shown in Figures 7 and 8. When the spacing member 32 is wound to a helical shape, a channel 33 will be formed between two contiguous turns to enclose the dialysis membrane 1. The open fibrous structure of the spacing member 32 is filled with the adsorbent A.

The spectrometer 12, Figures 1, 9 and 10, is a miniature spectrometer of simple design. It consists of a parallelepipedic frame 34, which is provided with a through hole 35 for a lamp 36, a filter 37 and a photoelectric cell 38. A second hole 39 is formed perpendicular to the hole 35 so that the transparent return hose 6 will intersect the light path between the lamp 36

and the photo-electric cell 38. The filter 37 is chosen to have an absorption typical of haemoglobin so that, when the absorption exceeds a certain pre-set value determined by safety reasons, the known electronic circuit will be activated by the spectrometer 12 to energise the buzzer 18 which then emits a warning signal.

The purification cartridge 11, shown in Figures 1 and 11, is formed as a cylindrical container, which contains the adsorbent A in a suitable, for example granular, state. The cartridge 11 is suspended vertically immersed into the dialysate 8 in the return hose 6 which is connected to a hose base provided on the upper end wall 40 of the cylindrical container. On the opposed end wall 42 of the purification cartridge 11, a short discharge pipe 41 is provided. In order to prevent the adsorbent from being flushed out, the end wall 42 is covered on the inside, as seen in Figure 1, with glass wool or fine-meshed cloth 49. Impurities in the dialysate 8 which are not adsorbed by the adsorbent in the spacing member 2, are adsorbed in the purification cartridge 11, so that the composition of the dialysate 8 will remain constant as dialysis proceeds. The adsorbent in the cartridge 11 can be recovered and regenerated if this is deemed economical.

The drop dosimeter 13, illustrated in Figures 1, 2 and 12, is located on the upper portion of the dialysate container 9 which comprises at least one, but preferably three to four pipe sockets 19 with external threads. A membrane 43 of rubber or another elastic material covers the mouth of the pipe socket 19 and is retained by a nut 44. A bottle 45 containing the additive to be metered is provided with an outwardly threaded neck and a cannula-shaped discharge pipe 46. This discharge pipe 46 is passed through the membrane 43, whereafter the bottle 45 is screwed into the nut 44. Adjustment of a valve (not shown in Figure 12) by means of a valve nut 47, allows an amount of air to pass into the bottle 45, and a corresponding volume of the additive to be metered out through the discharge pipe 46. Several designs of devices operating on this principle for sterile metering of a liquid are known.

According to an alternative embodiment (not shown) of the invention, the dialysis part of the apparatus is formed as a parallelepipedic dialysis container, which includes dialysis membranes and spacing members of the aforesaid kind as a battery of flat elements, i.e. in a way being usual among known dialyzers.

The dialysis apparatus according to the present invention achieves many advantages, partly by combining some

methods which were previously known individually, or in other combinations, in connection with dialysis and biochemistry, and partly by providing an apparatus of new and improved design. The factors contributing to the said good combinational effect are as follows:—

1. The apparatus is provided with a dialysis membrane, the pore size of which permits the passage of constituents with molecular weights up to between 10,000 and 15,000. Such membranes can be manufactured by known methods (Craig, L. C. and Koningsberg, W. J., Phys. Chem. 65, 166, 1961) of, for example, cellulose base, partially saponified cellulose acetate, copolymers of vinyl acetate and vinyl alcohol, homo- or copolymers of polymethyl-hydroxypropyl-, glycerol- or glycidyl methacrylate and of copolymers of acrylonitrile. Particularly suitable are those membrane materials, which are characterized by a certain hydrophily and the surface of which by hydrolysis, or other known methods, receives an increased amount of hydroxyl groups, which facilitates the method described later in item 2 for rendering the surface selectively chemically active. The increase of pore size for the dialysis of blood, from molecular weights of 2,500-3,000 as are possible with known apparatus, to 10,000-15,000 provides two advantages. Firstly the possibility of separating the aforementioned impurities which are incompletely known as to their composition and which have molecular weights from 3,000 up to 10,000-15,000, and secondly the shorter time required for the dialysis due to the increased pore size. The simultaneously arising disadvantage, that several important and desirable constituents of the blood having molecular weights below 10,000-15,000 can pass through the pores, is eliminated by the factors described later in items 3 and 4. As examples of constituents, which have molecular weights of up to 3,000 and are separated by known technique, can be mentioned ionizable or non-ionizable acids dissolved in water, salts, urica, creatinine and sugar types. For those cases in which it is considered sufficient to separate these substances and to refrain from the separation of the aforesaid impurities with molecular weights from 3,000 up to 10,000-15,000, the apparatus according to the invention can be provided with a dialysis membrane having the pore size applied in the known technique for a maximum molecular weight of 3,000 and yet obtain substantial advantages over known dialysis apparatus.

2. The surface of the dialysis membrane has been made selectively chemically active by insolubilizing at least one

chemically active substance on that side where the chemical activity is of interest. The active substances are enzymes and/or antibiotics, which by covalent bonds are very well insolubilized at the surface of the dialysis membrane. The method results both in a substantially longer active life of the substance in question and permits the use of active substances with antigen or other toxic effects in direct contact with blood when such use is motivated for therapeutical reasons, because nothing or only negligible amounts of the substance pass out in a free state into the blood. These properties just mentioned have been confirmed by clinical tests carried out for more than 2 years, at which tests an extracorporeal device constructed by the inventor and intended for enzyme therapy was used which is described in Arzneimittel-Forschung (Drug Research) 21, 1671-1675 (1971). At said tests it was found, that the enzyme L-asparaginase, which was insolubilized on a matrix in contact with blood in order to lower the asparagine content in the blood, has no appreciable antigen effect or other side effect on for example trombocytes, or by developing allergic conditions. Insolubilization of the selectively chemically active substance on the dialysis membrane surface facing toward the dialysate is of interest when impurities originating from the blood are to be removed from the dialysate in order to keep the composition of the dialysate constant. For example one can by the enzyme urease degrade urea to ammonium carbonate which in its turn is adsorbed as explained below in item 3. According to the aforesaid, this reaction can also be placed on the blood side of the dialysis membrane, but since urea passes without difficulties through the pores of the dialysis membrane, there is no reason for unnecessarily placing the enzyme reaction on the blood side. When, however, it is desired selectively to separate from the blood a substance, for example a protein, with a molecular weight so high that it cannot pass through the pores of the dialysis membrane, or can only do so with difficulty, then the enzyme must be insolubilized on the blood side. The intimate contact between the blood and the chemically active surface is favourable for the reaction. The degradation products have a low molecular weight and pass easily through the dialysis membrane to the dialysate where they are adsorbed as described below in item 3. The dialysis, therefore, proceeds rapidly. A group of substances which are considered responsible for some toxic symptoms at kidney failure, e.g. disturbances in the nervous system, are indole substances, indole, indican and other tryptophane derivatives.

By placing the selective chemical activity on the blood side of the dialysis membrane, such constituents and others can be removed from the blood by enzymatic degradation. Mycosis infections are a serious disease condition, which heretofore were difficult of access for effective treatment. Antibiotics are known which are highly effective against these fungus types. Unfortunately, they cannot be used in free form because they also are highly toxic. With a known method, however, an antibiotic can be insolubilized on a dialysis membrane of the aforesaid kind, at which the antibiotic with maintained chemical activity is insolubilized on the dialysis membrane by covalent bonds. The bonding to the dialysis membrane is very strong and, therefore, no antibiotic occurs in free form. By insolubilization of a suitable antibiotic on the blood side of the dialysis membrane in accordance with the invention, an effective and riskless form of therapy for mycosis infections is obtained. Enzymes, other proteins and antibiotics can be insolubilized on a carrier consisting of any one of the materials preferred in item 1 for the dialysis membrane by means of a well-known insolubilization method, for example the silanizing method or the cyanobromine method. The principle is described in detail in Weetall, H.H. and Weliky, N., Nature 204, 896, 1964, Porath J. Axen, R., and Ernback, S., Nature 215, 1491, 1967 and Mosbach, K., Acta Chem. Scand., 24, 2084, 1970.

3. The dialysate is purified continuously from the impurities passing through the dialysis membrane by means of adsorbents that are known in other connections and have a physical and chemical adsorbing effect, and wherever possible, have been made selective by known methods for the impurities in question. As examples of adsorbents of the kind concerned can be mentioned activated carbon and inorganic ion exchangers, zirconium phosphate and/or zirconium oxide specially preconditioned for this purpose. In order to improve the effectiveness, small cellulose balls are preferably used as carriers for the adsorbents. The adsorbents are arranged in the circulation system of the dialysate in the manner described below. In order to maintain the dialysate and the adsorbent moving relative to one another for facilitating the transport of those constituents in the dialysate which are to be adsorbed, the dialysis part of the apparatus is preferably provided in known manner with a vibrator, which may be small, simple and of optional type, but is preferably operated electrically. A suitable oscillation frequency is about 5-10 cycles per second. The composition of the di-

alysate can, by means of the adsorbents, be kept practically constant during a dialysis treatment. The adsorbents, and the apparatus details in which they are disposed, are intended to be discarded and replaced by new ones after each treatment. It is, therefore, of advantage that only a relatively small amount of an expensive substance, such as a zirconium preparation, is required for a treatment. It is, moreover, possible to regenerate the zirconium preparation according to known methods when such regeneration is economically viable. The greatest advantage of being able to maintain the composition of the dialysate constant is that it is possible, without deterioration of the dialysis result, to reduce the amount of necessary dialysate from 250-1,000 litres required for known techniques to a few litres, for instance, according to calculations and practical tests with an apparatus for haemodialysis to 3-5 litres. This has become possible partly because the apparatus according to the invention could be given the desired small dimensions and the desired simple design, and partly because the constituents which, as mentioned in item 1, are important for the blood and have a low molecular weight, and which are lost through the dialysis membrane, can be added to the dialysate at reasonable costs, so that said loss is balanced. It is, further, possible to add to the dialysate substances with molecular weights of about 8-9,000, for example a hormone, e.g. thyroglobulin or growth hormone for children.

4. The apparatus is provided with means in the form of at least one small and simple drop dosimeter disposed on the dialysate supply container for continuously adding to the dialysate the substances important for the blood as mentioned in items 1 and 3.

The effect of items 1-4 has made it possible to design dialysis apparatus according to the invention along lines which are entirely novel in several respects and provide essential advantages. The advantages resulting from the basic layout of the apparatus are briefly described as follows:—

The desire of obtaining a dialyzer in the form of a small, compact and easy-to-service unit has been satisfied, the container for the dialysate simultaneously serving as a stand for other components, which to the greatest possible extent are simplified and miniaturized, and are limited in number to what is absolutely necessary from an operational and safety point of view. The unit thus designed is a lightweight, transportable apparatus which, inclusive of the dialysate, has a weight of only 5-7 kg. and for its operation only requires to be connected to

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a normal mains socket. Alternatively, an electric battery can be mounted on the apparatus.

The principle requiring that, wherever possible, all medical equipment which involves the risk of spreading inoculation hepatitis to patients and medical staff members, should be disposable, is applied consistently. Only the dialysate container with the control and operation components attached thereon is intended for repeated use. The remaining components, which directly or indirectly come into contact with the blood, as well as those carrying the adsorbents are discarded after each treatment. A complete set of these latter components plus the necessary additives for the dialysate are, due to the small amounts and dimensions and the simple design, substantially cheaper than corresponding components for known dialyzers. The structural material in the apparatus according to the invention, if not specified otherwise, can be selected among materials which have already been tested in connection with dialyzers and heart-lung machines. The disposable portions are preferably made of some plastics material.

The feature that the dialysis membrane is given the form of a flattened tube and, together with an intermediate spacing and support member in the form of a flexible strip with open structure, is helically wound and located in a cylindrical container, provides several advantages. The blood and the dialysate can be led easily to and from the container by means of two connections per circuit and the circuits are preferably connected in counter-flow to provide maximum dialysis effect. It will become apparent from the following example, that the components disposed in and on the cylindrical container can be mounted in a simple manner with satisfactory sealing and without risk of leakage between the two circuits for the blood and the dialysate. As a practical example of the small dimensions of the apparatus, it can be mentioned that, if the dialysis membrane is given a total active surface of 0.99 m², the length is 2.08 m. and the distance between two adjacent membrane layers is 0.35 mm., then the total volume is 0.35 litre, about half of it being blood. The small blood amount in the apparatus, about 173—200 ml. is of advantage, because thereby no blood from a blood bank must be used for priming the system before its use nor must a blood substitute, for example Rheo-macrodex solution (Registered Trade Mark), be supplied to the patient. Blood remaining in the apparatus after the dialysis can easily be returned to the patient by adding an adjusted amount of a liquid neutral to the blood through the

blood supply hose. The blood loss arising at a dialysis treatment can in this manner be kept negligibly small. The blood and dialysate run in a laminar flow on both sides of the dialysis membrane, and the small distance, about 0.35 mm, between contiguous membranes implies a good contact between the liquids and the membrane, thereby facilitating the dialysis. A contributory factor is the vibrator mentioned in item 3. With the dimensions indicated above, the flow resistance of the blood will not exceed the difference in pressure which normally exists between an artery and a vein, and the necessary amount of blood, about 200 ml/min, will flow through the apparatus. The need of a blood pump is thereby eliminated in most cases.

For circulating the small volume of dialysate that is required, a small simple pump of optional type with associated electric motor is sufficient.

The adsorbents are provided both by being pressed into the open structure of the aforesaid distance and supporting member and in a separate purifying cartridge in the return line of the dialysate. Both these components with adsorbents are discarded after completed dialysis. The adsorbents being provided in two places, the purifying effect will be better and the safety greater. The purifying cartridge in the return line can, if this exceptionally should be necessary, be exchanged whilst the dialysis is going on.

In order, during dialysis, to supply to the dialysate adjusted amounts of the constituents that are important for the blood and have a molecular weight passing through the dialysis membrane, the supply container for the dialysis is provided with at least one and preferably several threaded pipe sockets, their mouths being covered with exchangeable elastic membranes. A known drop dosimeter which is formed as a bottle having an externally threaded neck and cannula-shaped outlet, is connected to one of the pipe sockets. The cannula is pierced through the elastic membrane, and the bottle is screwed into the pipe socket. The liquid additives can then be metered in a known manner.

The apparatus can also be provided with a safety device which, during dialysis, will emit an acoustic and/or optical signal whenever blood passes into the dialysate or when the patient is subjected to haemolysis, in both of which cases the dialysis must be interrupted. This safety device comprises a small and simple spectrometer which is disposed in or about the return line for the dialysate and incorporates a filter which is chosen so as to indicate absorption typical of haemoglobin.

The spectrometer is connected to operate an electronic alarm circuit of a known kind which includes a buzzer and/or a warning lamp.

For preventing the blood from cooling, the apparatus may be provided with a thermostat-controlled heating device which is preferably electric and is disposed in the supply container for the dialysate. The heating device can be completed by applying external insulation to the supply container by means of, for example, expanded polystyrene or glass wool.

During dialysis of blood, all surfaces coming into contact with the blood consist of known non-thrombogenic materials or are made non-thrombogenic in known manner by heparin bonded at the surfaces.

As an example of the efficiency of the apparatus, the result of four tests with an urea solution are reported below, the urea concentration being set to the high values which are observed in the blood during kidney insufficiency, that is 350 mg/100 ml.

For these tests dialysis apparatus according to the invention was used, the dimensions of which were reduced to laboratory test scale as follows:—

The dialysis membrane was of cellulose base with an active surface of 0.3 m², on a flat helically wound hose of 3.50 m. length. The distance between adjacent membranes was 0.5 mm. Urease was insolubilized on the membrane surface facing toward the dialysate (the outer system) with an urease solution containing 100 IU/ml. in a 10⁻²M. buffer solution, pH 7.3 according to a known method of Weetall and Weliky (loc. cit.). The inner system contained 500 ml. urea solution. 350 mg/100ml. 10⁻²M. buffer, pH 7.4 which circulated at 150 ml/min. The other system contained 1,000 ml. a counterflow at 380 ml/min. The apparatus, in order to obtain "pure" test values, 10⁻²M. buffer, pH 7.4 which circulated in did not contain adsorbents. The tests were carried out at room temperature. NH₄⁺ was measured with a cation-electrode, Beckmann 39137 and with an ammonium probe, 8002. The NH₄⁺ content was measured in the inner and outer solution during a dialysis time of 4h. The urea amount corresponding to the NH₄⁺ concentration was calculated in both solutions and summed up whereafter the mean values for the four tests were calculated. The urea concentration had after 4h. decreased from 350 to 180mg/100ml. The individual tests show a spread about the mean value of $\pm 18\text{mg}/100\text{ml}$.

If at the aforesaid test series an adsorbent preconditioned zirconium phosphate had been arranged in the outer system, which would have been the case

during dialysis treatment of blood *in vivo*, the adsorbent would have taken up the ammonium supplied at the dialysis. The dialysis thereby would have proceeded still faster at the same time as ammonium was transported from the inner to the outer system.

It will accordingly be appreciated that the present invention provides a dialysis apparatus in the form of a compact, complete, easily operated and cheap unit, which in suitable cases also can be used for home dialysis. Furthermore, the present invention achieves an improvement in the dialysis result.

The present invention also enables haemodialysis to be performed in a shorter time than is possible with known apparatus. It also makes possible the separation from the blood of incompletely known impurities with a high molecular weight, up to 10,000-15,000. The present invention also combines dialysis through a semipermeable membrane with chemical activity on the dialysate side of the membrane in order to purify the dialysate.

The present invention furthermore combines dialysis through a semipermeable membrane with chemical activity on the blood side of the membrane in order selectively, and without toxic side-effects, to affect both the liquid phase of the blood and the blood cells for achieving a therapeutical effect at different pathological conditions. The dialysis apparatus is also designed so that it involves the smallest possible risk of spreading inoculation hepatitis. The present invention also prevents the coagulation of blood in the dialysis apparatus.

WHAT I CLAIM IS:

1. Dialysis apparatus with selective chemical activity, such as an artificial kidney, including a semipermeable dialysis membrane forming a partition between the liquid to be dialyzed and a dialysate, the dialysis membrane being selected to permit the passage of substances with molecular weights of at least 2,500, a first surface of the dialysis membrane facing the dialyzed liquid, a second surface of the dialysis membrane facing the dialysate, at least one of said surfaces being coated with at least one selectively chemically active substance insolubilized on the surface, and at least one selectively acting adsorbent being provided in the circuit of the dialysate.
2. Dialysis apparatus, according to Claim 1, in which the dialysis membrane is selected to permit the passage of substances with molecular weights of up to 10,000.

3. Dialysis apparatus, according to Claim 1, in which the dialysis membrane is selected to permit the passage of substances with molecular weights of up to

15,000.

4. Dialysis apparatus, according to any preceding Claim, in which the chemically active substance is an enzyme or other protein, or an antibiotic.

5. Dialysis apparatus, according to any preceding Claim, in which the dialysis membrane is in the form of a flattened tube, a spacing member has an open structure carrying an adsorbent or a mixture of adsorbents, and the dialysis membrane and the spacing member are wound helically together.

6. Dialysis apparatus, according to any of Claims 1 to 4, in which the dialysis membrane is of a flat shape and placed adjacent a spacing member of similar shape.

7. Dialysis apparatus, according to any preceding claim, in which the dialysis membrane consists of a material of which the surface is so prepared that it shows an increased number of hydroxyl groups or other groups for rendering possible the insolubilization of enzymes or antibiotics.

8. Dialysis apparatus, according to Claim 5 or 6, in which the spacing member consists of a base provided with fine perforations and an open support and spacing structure secured to the base which defines ridges extending at an oblique angle to the longitudinal direction of the spacing member.

9. Dialysis apparatus, according to Claim 5 or 6, in which the spacing member is formed as a plastics-bonded, thin, flexible beam with a generally I-shaped cross-section moulded from a fibrous material.

10. Dialysis apparatus, according to any preceding Claim, in which the adsorbent consists of pre-conditioned zirconium phosphate and/or zirconium oxide.

11. Dialysis apparatus, according to any of Claims 1 to 9, in which the adsorbent consists of pre-conditioned zirconium phosphate and/or zirconium oxide in combination with activated carbon.

12. Dialysis apparatus, according to any preceding Claim, in which a purifying cartridge containing the adsorbent is provided in a return flowpath of the dialysate.

13. Dialysis apparatus, according to any preceding Claim, in which at least one drop dosimeter is provided for the supply of additives to the dialysate.

14. Dialysis apparatus, according to any preceding Claim, in which the dialysis container is provided with a vibrator.

15. Dialysis apparatus, according to any preceding claim, which is formed as a compact transportable unit, in such a manner, that a container for the dialysate carries the remaining main components of the apparatus.

16. Dialysis apparatus constructed and arranged and adapted to operate substantially as described herein and as shown in the accompanying drawings.

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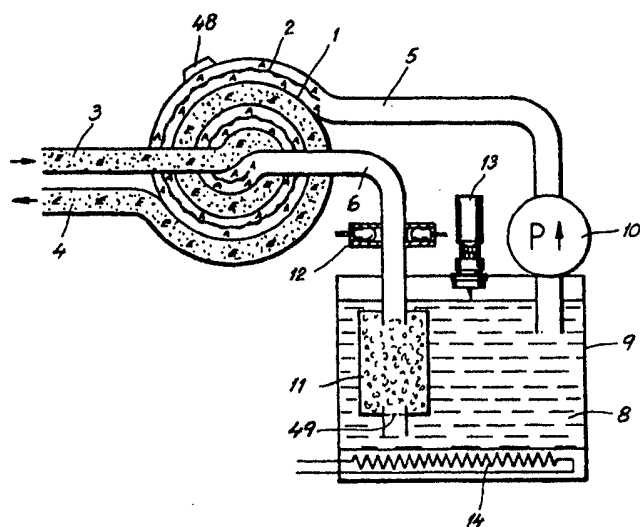


Fig.1

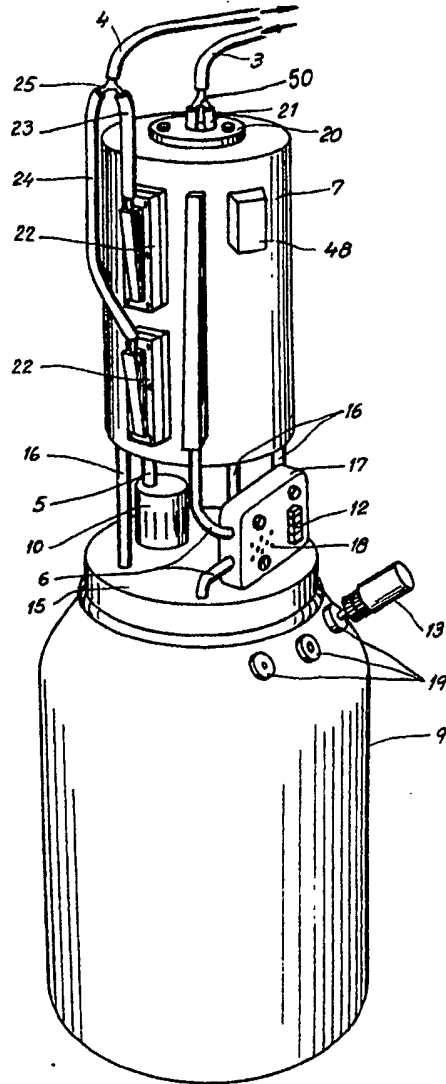


Fig.2

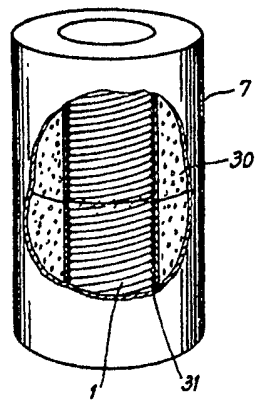


Fig. 3

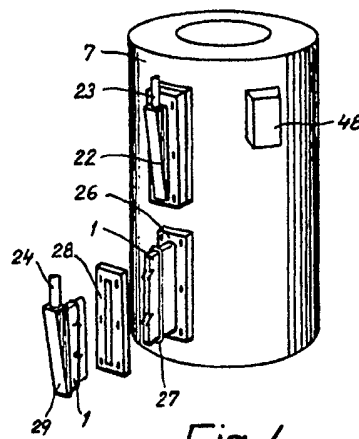


Fig. 4

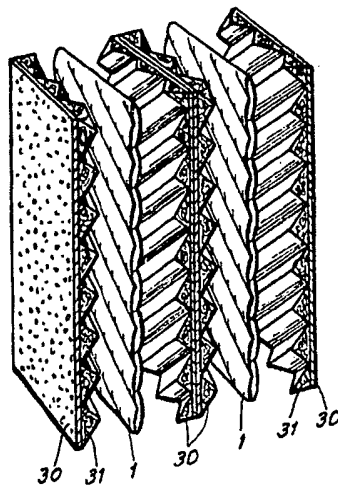


Fig. 5

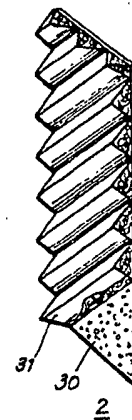


Fig. 6

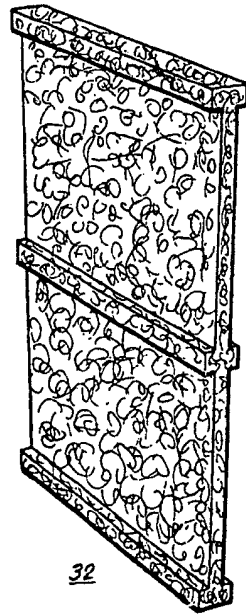


Fig. 7

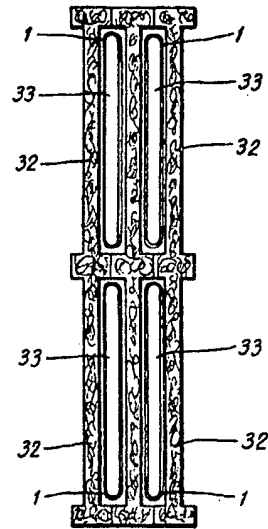


Fig. 8

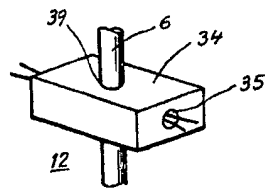


Fig. 9

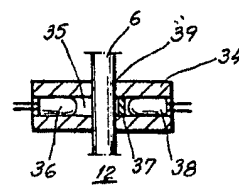


Fig. 10

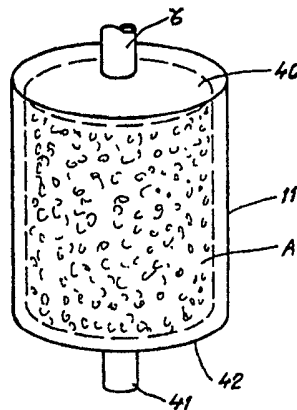


Fig. 11

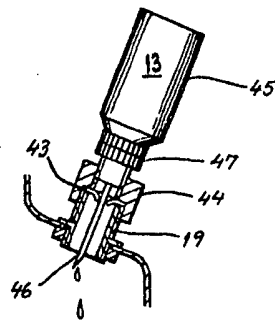


Fig. 12